**How Toxicity Pathways Become Virtual Screening Models**

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**Key Words:** QSAR, endocrine disrupting chemical, estrogen, computational toxicology, toxicity pathways

One of the greatest opportunities to reduce animal testing is to minimize the number of tests required by EPA on inactive chemicals. The use of quantitative structure-activity relationships (QSAR) is the most common *in silico* method used to strategically focus testing resources on active chemicals. Virtual screening with QSAR is simplest when the hazard is clearly identified and the toxicity pathway is known. EPA faces many prioritization needs involving reproductive and developmental hazards which can result from a variety of partially understood pathways. One such need is the identification of endocrine disrupting chemicals (EDC) from among the tens of thousands of chemicals in commerce. There are numerous pathways through which chemicals could disrupt the endocrine system and cause reproductive or developmental impairment in animal populations, and ORD has a core research program to understand them. The Computational Toxicology program seeks to translate the understanding of toxicity pathways into computerized screening tools which can rapidly screens thousands of chemicals for their potential to cause the specific molecular perturbations leading to reproductive and developmental impairment. Using the QSAR approach, the toxicity pathways for EDC are divided into the estrogen, androgen and thyroid pathways, each of which appear to have receptor-based and enzyme inhibition initiating possibilities. For example, binding of chemicals to the estrogen receptor (ER) is a major initial event in endocrine disruption, and estimating ER binding affinity by computerized QSAR can rapidly identify chemicals from inventories most likely to be active in subsequent tests with animals. However, virtual screening methods must define both the structural requirements for receptor binding as well as the binding energies at the receptor in terms of molecular descriptors which can be computed for all chemicals to be screened for EDCs. Recent advances in 3-D modeling of chemical structures make *in silico* methods for estimating ER binding and most other important chemical interactions possible. A scheme for iterative QSAR model development is presented that allows for model development, assessment, and improvement through a series of steps, following rigid scientific criteria, until the model is determined acceptable for regulatory use.

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